

Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell Aging Medicine

幹細胞加齢医学分野

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Stem cell systems play fundamental roles in sustaining tissue turnover and homeostasis. Our goal is to understand the mechanisms of tissue aging and cancer development in mammals and to apply that knowledge to develop strategies to resist against tissue/organ aging, cancer development and other relevant diseases associated with aging. We further aim to apply this knowledge to drug discovery and the prevention and treatment of age-associated diseases.

1. Stem cell fate governs hair graying and melanoma development

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The accumulation of an individual's lifelong environmental exposure, known as the "exposome", has a significant impact on health. Somatic tissues undergo functional decline with age, exhibiting characteristic ageing phenotypes such as hair graying and cancer. However, specific genotoxins and signals driving each phenotype and their underlying cellular mechanisms remain largely unknown. Importantly, DNA damage foci are relatively frequently found in somatic stem cells in the skin during physiological aging. Using a DNA damage inducing model, we previously found that the induction of DNA double strand breaks (DSBs) advances the expression of aging phenotypes including hair graying. To study the fate and dynamics of DNA-damaged stem cells in tissues and the resultant impact in the expression of aging phenotypes, we first focused on the melanocyte lineage and traced the fate of melanocyte stem cells (McSCs) which acquired DNA DSBs and demonstrated that those cells disappear from the niche, causing the loss of mature melanocytes for hair pigmentation.

We studied the impact of DSBs in McSCs and found that McSCs and their niche coordinately determine individual stem cell fate through antagonistic, stress-responsive pathways, depending on the type of genotoxic damage incurred. Chronological stem cell fate-tracking in mice revealed that McSCs undergo

cellular senescence-associated differentiation (seno-differentiation) in response to DSBs and downstream signaling, resulting in their selective depletion and hair graying, effectively acting as a protective mechanism against melanoma development. Conversely, carcinogens can suppress McSC seno-differentiation, even in DSB-harboring cells, by activating KITL (KIT ligand), a master niche factor for McSC self-renewal. Collectively, our data demonstrate that the fate of individual stem cell clones - expansion versus exhaustion - cumulatively and antagonistically governs a degenerative ageing phenotype and/or cancer development through the stem cell niche, depending on the exposome. We are currently testing whether DNA DSBs in other stem cells similarly promotes degenerative tissue aging.

2. Fate tracing of hair follicle stem cells and their seno-differentiation clearance out of the niche

Miranda-Salmeron M¹, Higa M¹, Matsumura H¹, Muroyama Y¹, Kato T², Tan L¹, Kawamura Y¹, Namba D¹, Mohri Y¹, and Nishimura EK¹.

Hair follicles, mammalian mini-organs that grow hair, miniaturize during aging, leading to hair thinning and loss. In the event of severe genotoxicity such as DNA double-strand breaks (DSBs), stem cells are largely believed to choose between cell death (apoptosis) or irreversible cell cycle arrest (senescence) to

prevent further damage to neighboring healthy cells and tissues. Accumulation of these senescent cells across organs has been implicated in disease and aging-related morbidities such as cancer and frailty. However, the exact fate and dynamics of sublethally damaged cells in tissues during aging/chemotherapy and the development of alopecia and where exactly senescent cells exist in tissues are still largely unknown because of the lack of any single perfect marker of senescent cells. Previous work from our group demonstrated that various stem cells in the skin will aberrantly commit to differentiation in response to DNA damage by abrogating their self-renewal capabilities to discard unfit/stressed/aged stem cells. We are testing the unique hypothesis that the tissue youth is achieved through rapid, dynamic clearance of DNA-damaged cells out of the epithelia as a robust genomic quality control mechanism. We are evaluating a combination of recently devised mouse lines that can induce DSBs in a small number of stem cells to visualize and trace the exact fate, senescent state, and dynamics of those individual cells in epithelial tissue such as the hair follicle. We are in the process of characterizing the identity of those DNA-damaged HFSCs and their fate switching in the HFSC niche that leads to hair follicle miniaturization and hair loss. Taken together, our findings demonstrate a tissue-autonomous mechanism within the hair follicle niche that can effectively discard DNA-damaged cells.

Publications

1. Yang JH, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, Salfati EL, Blanchette M, Munding EM, Bhakta M, Chew YC, Guo W, Yang X, Maybury-Lewis S, Tian X, Ross JM, Coppotelli G, Meer MV, Rogers-Hammond R, Vera DL, Lu YR, Pippin JW, Creswell ML, Dou Z, Xu C, Mitchell SJ, Das A, O'Connell BL, Thakur S, Kane AE, Su Q, Mohri Y, Nishimura EK, Schaevelt L, Garg N, Balta AM, Rego MA, Gregory-Ksander M, Jakobs TC, Zhong L, Wakimoto H, El Andari J, Grimm D, Mostoslavsky R, Wagers AJ, Tsubota K, Bonasera SJ, Palmeira CM, Seidman JG, Seidman CE, Wolf NS, Kreiling JA, Sedivy JM, Murphy GF, Green RE, Garcia BA, Berger SL, Oberdoerffer P, Shankland SJ, Gladyshev VN, Ksander BR, Pfennig AR, Rajman LA, Sinclair DA. Loss of epigenetic information as a cause of mammalian aging. *Cell*. 186(2): 305-326, 2023
2. Kato, T. Liu, N. Morinaga, H. Asakawa, K. Muroguchi, T. Muroyama, Y. Shimokawa, M. Matsumura, H. Nishimori, Y. Tan, L.J. Hayano, M. Sinclair, DA. Mohri, Y. Nishimura, EK. Dynamic stem cell selection safeguards the genomic integrity of the epidermis. *Dev Cell*. 56: 3309-3320, 2021